

REMARKS

In view of the following remarks, the Examiner is respectfully requested to withdraw the rejections and allow claims 15-20, 26-28, and 30-47, the only claims pending and currently under examination in this application.

Claim 29 has been canceled.

Claims 15, 16, 30, 31, have been amended. Support for the amendments can be found in the claims as originally filed and throughout the specification at, for example, claim 15: original claim 29; page 17, paragraph [0078], page 10, paragraph [0046]; claim 16: page 14, paragraphs [0064] to [0066], and paragraph [00134] bridging pages 31 and 32; claim 30: page 17, paragraph [0078], page 10, paragraph [0046]; and claim 31: page 14, paragraphs [0064] to [0066].

New claims 39-47 have been added. Support for new claims 39-47 is found in the claims as originally filed and throughout the specification at, for example, original claims 15 to 20 and 26 to 29; and page 17, paragraph [0078], page 10, paragraph [0046]; page 13, paragraph [0063], and page 11, paragraph [0048].

Accordingly, no new matter is added.

Rejections and objections of Office Action dated November 4, 2003

The Applicants acknowledge with gratitude the Examiner's indication that the objections to the specification and the claims, and rejections under 35 U.S.C. § 112, second paragraph, and 35 U.S.C. § 102, as set forth in the Office Action dated August 26, 2003 have been withdrawn.

Priority

The Office Action asserts that the disclosure of the genus of claims 15-20 and 26-28 is not present in either of the priority applications. In particular, the Office Action states that while the disclosure of claim 29, where $n=6$, and claim 30 are found in Figure 3 of U.S. Application No. 60/101,867, filed on September 25, 1998, the disclosure of the

genus of claims 15-20 and 26-28 is not present in the priority documents. Accordingly, the Office Action concludes that claims 15-20 and 26-28 are afforded an earliest effective filing date of May 15, 2001, the filing date of the instant application, and claims 29-38 are afforded an earliest effective filing date of September 25, 1998.

The Applicants note that both U.S. Application Nos. 60/101,867 and 09/404,017 disclose metal ion affinity peptides, fusion proteins comprising the metal ion affinity peptides, as well as polynucleotides encoding fusion proteins comprising the metal ion affinity peptides. The disclosed metal ion affinity peptides include peptides comprising of the following formula $(\text{His-Asn})_n$, as well as $(\text{His-X}_1\text{-X}_2)_{n1}\text{-(His-X}_3\text{-X}_4\text{-X}_5)_{n2}\text{-(His-X}_6)_{n3}$. However, in the spirit of expediting prosecution and without conceding to the correctness of the priority determination, the Applications have amended claim 15 to recite **"NH₂-(His-Asn)_n or (His-Asn)_n-COOH, where n=6"**. Accordingly, claims 15-20 and 26-28 should be afforded the earliest effective filing date of September 25, 1998.

Compliance with Sequence Listing

Enclosed with this response please find a substitute copy of the sequence listing in both paper and computer readable form. Above please find an amendment requesting its entry into the present application, in place of all previously filed sequence listings.

I hereby certify that the enclosed substitute Sequence Listing is being submitted under 37 CFR §§ 1.821(c) and (e) in paper and computer readable form (Compact Disk labeled 'CRF').

As required by 37 CFR 1.821(f), I hereby state that the content of the paper and computer readable copy of the Sequence Listing, submitted in accordance with 37 C.F.R. §1.821(c) and (e) are the same. The Computer Readable Format (CRF), being submitted under 37 CFR §§ 1.52(e) and 1.824, is formatted on IBM-PC, the operating system compatibility is MS-Windows and the file listing is:

Sequence Listing.txt 13.4 KB created August 5, 2004.

Objections to the Specification

Abstract

The Office Action has maintained the previous objection to the abstract. Specifically, the Office Action states that the abstract should be a single paragraph, without the inclusion of claim-like indentation. It is believed that the above amendments to the abstract overcome the objection raised by the Office Action thereto.

Specification – Compliance with Sequence Rules

The Office Action notes the following objections to the sequence listing filed on March 3, 2004:

- The 5-mer polypeptide of paragraph 20 is disclosed without the benefit of SEQ ID NO;
- Three polypeptides in Figure 2B in addition to SEQ ID NO:14, are disclosed without the benefit of SEQ ID NOs;
- The DNA of Figure 2 is described in the specification as 3426 base pairs long; however, the SEQ ID NO:13 in the sequence listing is 3430 base pairs long;
- Paragraph [0011] of the specification describes the sequence of Figure 3 as SEQ ID NO:28, but should be SEQ ID NO:18;
- The 18-mer polypeptide of Figure 3, also described in paragraph [0063], is described as SEQ ID NO:03; however, SEQ ID NO:03 is a 16-mer polypeptide;
- The sequences described in paragraphs [0068] and [0069] are all incorrect; and
- SEQ ID NO:11 and SEQ ID NO:12 are identical.

It is believed the above amendments to the specification and the new sequence listing provided herewith address all of the Examiner's objections.

35 U.S.C. § 112, second paragraph

Claims 16 and 31

The Examiner has rejected claims 16 and 31 under 35 U.S.C. § 112, second paragraph for allegedly being unclear. Claims 16 and 31 have been amended to recite a “polynucleotide comprises a nucleotide sequence **encoding** a fusion protein comprising a polypeptide **and** the metal ion affinity peptide, **wherein the metal affinity peptide is fused to an amino- or carboxy terminal amino acid of the polypeptide.**” Support for the amendments can be found in the claims as originally filed, and throughout the specification at, for example, page 14 paragraph [0064] and paragraph [00134] bridging pages 31 and 32. Accordingly, in view of the amendments to the claims, the Applicants respectfully request that this rejection be withdrawn.

Claims 15-20 and 26-28

The Examiner has also rejected claims 15-20 and 26-28 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter regarded as the invention. In particular, the Examiner notes that the position of the sequence ID reference in claim 15 is confusing. Claim 15 has been amended to remove the “SEQ ID NO:22”. Accordingly, in view of the amendments to the claims, this rejection is rendered moot.

Claims 30-38

The Examiner has also rejected claims 30-38 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter regarded as the invention. In particular, the Examiner states that the use of the use of “NH₂” and “COOH” is confusing, since reciting both an N-terminus and C-terminus tag appears to close the claim since no other polypeptide sequence would be attached. Claim 30 has been amended to recite “having the amino acid sequence **NH₂-His-Leu-Ile-His-Asn-Val-His-Lys-Glu-Glu-His-Ala-His-Ala-His-Asn or His-Leu-Ile-His-Asn-Val-His-Lys-Glu-Glu-His-Ala-His-Ala-His-Asn-COOH.**” Accordingly, in view of the amendments to the claims, the Applicants respectfully request that this rejection be withdrawn.

35 U.S.C. § 101

The Office Action has rejected claims 15 and 17-20 under 35 U.S.C. § 101 as allegedly claiming non-statutory subject matter. In particular, the Office Action asserts that claims 15 and 30 do not sufficiently distinguish over polynucleotides as they naturally exist. This rejection is respectfully traversed.

Claims 15 and 30 have been amended to recite formulas that includes either a NH_2 - or a $-\text{COOH}$. Support for the amendments is found in the claims as originally filed and throughout the specification at, for example, page 17, paragraph [0078], and page 10, paragraph [0046]. Accordingly, since the metal ion affinity tags encoded by polynucleotides of claim 15 and 30 are terminal peptides, the claims specifically point out a non-naturally occurring difference between the claimed products and naturally occurring products. Therefore, the Applicants respectfully request that this rejection be withdrawn.

35 U.S.C. § 102

Sato et al.

Claims 15 and 17-20 have been rejected under 35 U.S.C. §102(e) as allegedly being anticipated by Sato et al. (U.S. Patent Application 2003/0079237). As discussed above, claims 15 and 17-20 are fully entitled to the priority date of September 25, 1998. Accordingly, the cited Sato et al. reference is not available as prior art to the present claims 15 and 17-20 and this rejection may be withdrawn

With respect to new claims 39-47, claim 39 recite a " NH_2 -(His-Asn)_n or (His-Asn)_n-COOH." Therefore, claim 39 is directed to an N- or C-terminal metal ion affinity tag that includes either a free NH_2 or a free $-\text{COOH}$. Support for the amendment is found in the claims as originally filed and throughout the specification at, for example, page 17, paragraph [0078], and page 10, paragraph [0046].

As noted in the Office Action, Sato et al. discloses a nucleic acid molecule that includes an internal His-Asn-His-Asn-His-Asn fragment. Accordingly, the cited

reference fails to disclose a His-Asn-His-Asn-His-Asn fragment that includes either a free NH₂ or a free -COOH. Therefore, since the cited reference does not teach each and every limitation found in the claim, the cited reference fails to anticipate new claims 39-47.

CLONTECHniques, October 1999

Claims 15-19 and 26-28 have been rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by CLONTECHniques (PROTet™ 6xHN Bacterial Expression System, October, 1999, pages 23-24) (hereinafter "CLONTECHniques, October 1999"). As discussed above, the claims are fully entitled to the claimed priority date of September 25, 1998. Therefore, the cited CLONTECHniques, October 1999, reference is not available as prior art to claims 15-19 and 26-29 and the this rejection may be withdrawn.

With respect to new claims 39-47, claim 39 recites a "NH₂-(His-Asn)_n or (His-Asn)_n-COOH, where n=3-5 or 7-10." Therefore, claim 39 is directed to an N- or C-terminal metal ion affinity tag having a formula of (His-Asn)_n, where n= 3-5 or 7-10. Support for the amendments is found in the claims as originally filed and throughout the specification at, for example, page 13, paragraph [0063], which describes a range of 3 to 10 subunits of (His-Asn), and page 11, paragraph [0048], which discloses that "where a range of values is provided, it is understood that each intervening value...between the upper and lower limit of that range and any other stated or intervening value in that stated range, is encompassed within the invention."

CLONTECHniques, October 1999, specifically discloses an inducible bacterial expression system that includes a 6xHN (i.e., His-Asn- His-Asn- His-Asn- His-Asn- His-Asn- His-Asn or (His-Asn)x6) tag. The disclosure of the cited reference is limited to a 6x(His-Asn) tag. Nowhere does the cited reference disclose that any other number of (His-Asn) subunits may be successfully used. Accordingly, the cited reference fails to disclose a metal ion affinity tag having a formula of (His-Asn)_n, where n= 3-5 or 7-10. Therefore, since the cited reference does not teach each and every limitation found in the claim, the cited reference fails to anticipate claims 39-47.

Hirota et al.

Claims 30-33 have been rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Hirota et al., 1990 Nuc. Acid Res., 18:21 (hereinafter Hiro et al.). This rejection is respectfully traversed.

As noted in the Office Action, Hirota et al. discloses a nucleic acid molecule that includes an internal His-Leu-Ile-His-Asn-Val-His-Lys-Glu-Glu-His-Ala-His-Ala-His-Asn fragment., nowhere does Hirota et al. disclose that the fragment may be located at the N- or C-terminus of a polypeptide, where the His-Leu-Ile-His-Asn-Val-His-Lys-Glu-Glu-His-Ala-His-Ala-His-Asn fragment would include a free NH₂- or a free -COOH. Moreover, nowhere does Hirota et al. disclose that the His-Leu-Ile-His-Asn-Val-His-Lys-Glu-Glu-His-Ala-His-Ala-His-Asn fragment is a metal ion affinity peptide for a downstream or upstream sequence. Such is simply not disclosed in the cited reference.

In contrast, newly amended claim 30 recites a “NH₂-His-Leu-Ile-His-Asn-Val-His-Lys-Glu-Glu-His-Ala-His-Ala-His-Asn or His-Leu-Ile-His-Asn-Val-His-Lys-Glu-Glu-His-Ala-His-Ala-His-Asn-COOH.” Therefore, claim 30 is directed to an N- or C-terminal metal ion affinity tag. Support for the amendments is found in the claims as originally filed and throughout the specification at, for example, page 17, paragraph [0078], and page 10, paragraph [0046].

Accordingly, the cited reference fails to disclose a His-Leu-Ile-His-Asn-Val-His-Lys-Glu-Glu-His-Ala-His-Ala-His-Asn fragment that includes either a free NH₂- or a free -COOH. Since the cited reference does not teach each and every limitation found in the claim, the cited reference fails to anticipate claims 30-33. Therefore, the Applicants respectfully request that this rejection be withdrawn.

CLONTECHniques, July 1998

Claims 30-34 and 36-38 have been rejected under 35 U.S.C. § 102(a) as allegedly being anticipated by CLONTECHniques (HAT™ Protein Expression &

Purification System, July 1998) (Hereinafter "CLONTECHniques, July 1998"). This rejection is respectfully traversed.

The enclosed Declaration under 37 C.F.R. §1.131 demonstrates that the claimed subject matter of the present application was invented by the inventors prior to July 1998.

As set forth in 37 C.F.R. §1.131:

(a) When any claim of an application or a patent under reexamination is rejected, the inventor of the subject matter of the rejected claim, the owner of the patent under reexamination, or the party qualified under §§1.42, 1.43, or 1.47, **may submit an appropriate oath or declaration to establish invention of the subject matter of the rejected claim prior to the effective date of the reference** or activity on which the rejection is based. . . .

(b) **The showing of facts shall be such, in character and weight, as to establish reduction to practice prior to the effective date of the reference**, or conception of the invention prior to the effective date of the reference coupled with due diligence from prior to said date to a subsequent reduction to practice or to the filing of the application. . . . (emphasis added)

As such, a 35 U.S.C. §102(a) rejection may be withdrawn if the Applicants can establish, by means of a declaration and a showing of facts, that the claimed subject matter was invented prior to the effective date of the cited reference.

In order to establish that the claimed invention was invented prior to the July 1998 priority date of the cited reference, the Applicants submit herewith the Declaration of Grigoriy S. Tchaga and George G. Jokhadze under 37 C.F.R. §1.131. This declaration provides a showing of facts that the inventors invented the claimed invention prior to the July 1998 effective priority date of the cited reference in that the inventors had invented compositions and methods of incorporating a polyhistidine metal ion affinity sequence at the N-or C-terminal sequence of recombinant proteins for the purification of the recombinant proteins prior to the effective date of July 1998 of the cited reference.

Since the Applicants have provided a declaration and facts that show invention prior to the effective date of the cited reference, the rejection of claims 30-34 and 36-38 under 35 U.S.C. §102(a) may be withdrawn.

CONCLUSION

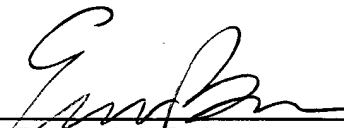
In view of the above amendments and remarks, this application is considered to be in good and proper form for allowance and the Examiner is respectfully requested to pass this application to issue.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16 and 1.17 which may be required by this paper, or to credit any overpayment, to Deposit Account No. 50-0815.

Respectfully submitted,

BOZICEVIC, FIELD & FRANCIS LLP

Date: 8.19.04

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